REMARKS

I. The Amendments

The claims have been amended for the purpose of more clearly defining what Applicants regard as the invention. Specifically, Claims 4, 5, 25, 26, 39, and 40 have been amended to correct their dependency. Further, the claims have been amended to correct some grammatical inconsistencies. The amendments do not introduce new matter and they are fully supported by the Specification of the present application and the claims as originally filed. Entry of the amended claims under 37 C.F.R. §1.111 is respectfully requested.

Instructions for amending the claims are attached hereto as *Appendix B.* The claims as pending after entry of the instant amendments are attached hereto as *Appendix C.*

II. Withdrawn Rejections

Applicants note with appreciation that the rejection of Claim 14 under 35 U.S.C. §101 for allegedly improperly defining a process has been withdrawn.

Applicants further note with appreciation that the rejection of Claims 14, 20, 21, 22, 30, 37, and 43 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite, has been withdrawn in view of Applicants amendments and arguments.

Applicants further note with appreciation that the rejection of Claim 43 under 35 U.S.C. §112, first paragraph, for allegedly lacking written description, has been withdrawn in view of Applicants arguments.

Applicants further note with appreciation that the rejection of Claims 4, 15-18, 23-27, 30, 35-37, 42 and 43 as allegedly anticipated under 35 U.S.C. §102(b) over

U.S. Pat. No. 4,731,439 to Marquardt *et al.* ("the '439 patent") has been withdrawn in view of Applicants arguments.

Applicants further note with appreciation that the rejection of Claims 23 and 30 under 35 U.S.C. §102(b) over Blair *et al.*, 1983, *J. Immunological Methods* 59:129-43 ("Blair") has been withdrawn in view of Applicants arguments.

Finally, Applicants note with appreciation that the rejection of Claims 4, 5, 15-17, 19, 21, 22, 28, 29, 31-34 and 38-41 under 35 U.S.C. §103(a) over one or more combinations of the '439 patent, Blair, U.S. Pat. No. 5,116,944 to Sivam *et al.* ("the '944 patent"), U.S. Pat. No. 5,169,934 to Clark *et al.* ("the '934 patent"), Sezaki *et al.*, 1984, *Critical Rev. Therapeutic Drug Carrier Systems* 1:1-38 ("Sezaki"), Oseroff *et al.*, 1986, *Proc. Natl. Acad. Sci. U.S.A.* 83:8744-48 ("Oseroff") and U.S. Pat. No. 4,522,750 to Ades *et al.* ("the '750 patent") has been withdrawn in view of Applicants arguments.

III. The Rejections

A. Double-Patenting Rejection

Claims 4, 5 and 15, 17, 18, 20-27, 30-40, 42, and 43 are provisionally rejected under 35 U.S.C. §101 for allegedly being identical to claims in co-pending United States patent application Serial No. 09/641,026 (the "'026 application"). This rejection is moot in view of the abandonment of the '026 application. *See*, Notice of Abandonment mailed June 18, 2002 in the '026 application (Paper No. 4), for the Examiner's convenience attached hereto as *Exhibit 1*.

In view of the above, it is respectfully requested that the double patenting rejection of Claims 4, 5, 15, 17, 18, 20-27, 30-40, 42, and 43 be withdrawn.

B. Rejection of Claims 4, 5, 25, 26, 39, and 40 Under 35 U.S.C. §112, Second Paragraph

Claims 4, 5, 25, 26, 39, and 40 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for being dependent on canceled Claim 16. The claims have been amended to recite the proper dependency. The rejection should therefore be withdrawn.

C. Rejection of Claims 4, 5, 15, 17, 18, 23, 26, 27, 32, 38, 42, and 43 Under 35 U.S.C. §103(a)

Claims 4, 5, 15, 17, 18, 23, 26, 27, 32, 38, 42, and 43 are rejected under 35 U.S.C. §103(a) as being obvious over Srinivasan *et al.*, U.S. Patent No. 5,066,789 ("Srinivasan"), in view of Spector *et al.*, U.S. Patent No. 3,976,763 ("Spector") and Wong, 1991, *Chemistry of Protein Conjugation and Cross-Linking*, CRC Press, pp. 63-67 ("Wong"). The rejection is respectfully traversed.

The Applicable Law. In rejecting the claimed invention, the law is clear that ***the prior art must contain some suggestion***, either explicit or implicit, of the combination proposed by the Examiner in order to render an invention obvious. *See, e.g.*, In re Sernaker, 217 USPQ 1 (Fed. Cir. 1983); In re Grabiak, 226 USPQ 870 (Fed. Cir. 1985); In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988); Panduit Corp. v. Denisson Manufacturing Co., 1 USPQ2d 1593, 1597 (Fed. Cir. 1987); In re Nilssen, 7 USPQ 2d 1500 (Fed. Cir. 1988). Or as it is set forth in Ex parte Dussaud, 7 USPQ 2d 1818, 1820 (1988):

> In our view, however, such proposed modification amounts to a hindsight reconstruction of the prior art patents in order to arrive at appellant's invention. Without having the benefit of appellant's disclosure [...] the artisan would [not] have found it obvious [...]

> We have carefully reviewed the [cited] references in their entireties, and we find ***no express or implied suggestion in the collective teachings which would have motivated the artisan to combine them in the manner proposed***. (emphasis added).

Furthermore, as set forth by the Board of Appeals and Interferences in Ex Parte Levengood, 28 USPQ2d 1300 (1993), no *prima facie* case of obviousness can be established without some objective reason to combine the teachings of the references; the mere fact that all aspects of the claimed invention were individually known in the art is not sufficient. Specifically, the Board stated:

> That one can ***reconstruct*** and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of the ordinary skill in the art to combine the teachings of the references to make the claimed invention.

Moreover, as stated by the CAFC in In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-1532 (Fed. Cir. 1988), the cited art must provide some reasonable expectation of success that the invention would work:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success....[citation] ***Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure***. (emphasis added)

The Office Action fails to establish either prong of the obviousness standard. The cited references taken together as a whole do not suggest the claimed invention, nor would they provide reasonable expectation of success that the Applicants' invention would work. First, the cited references as a whole do not teach or suggest a

conjugate comprising (a) an active substance useful for treating said disease selected from the group consisting of a chemotherapeutic agent and a photoactive compound, (b) a native human serum albumin that is not regarded as exogenous by the subject, and (c) a linker linking the active substance to the albumin, wherein the linker can be cleaved intracellularly, and wherein the linker comprises an azo group. Second, the cited art does not provide reasonable expectation that the presently claimed invention could be successfully made. The Office Action also fails to establish that the cited references contain reason to combine the teachings found therein, short of providing motivation to make the presently claimed invention.

More specifically, and with respect to the points raised in the Office Action, Applicants offer the remarks set forth in the following.

The Presently Claimed Invention. The presently claimed invention is directed to a conjugate useful for treating a tumoral, infectious, or autoimmune disease in a subject. The claimed conjugate comprises (a) an active substance useful for treating said disease selected from the group consisting of a chemotherapeutic agent and a photoactive compound, (b) a native human serum albumin that is not regarded as exogenous by the subject, and (c) a linker linking the active substance to the albumin, wherein the linker can be cleaved intracellularly, and wherein the linker comprises an azo group. *See*, Claim 15. The invention is further directed to a process of preparing such conjugate, and to a method of treatment using such conjugate.

The Cited References Do Not Suggest the Claimed Invention. Applicants respectfully submit that the combination of the cited references, *i.e.*, Srinivasan, Spector and Wong do not teach or suggest the presently claimed invention. In particular, the cited references, *inter alia*, do not teach or suggest a conjugate

comprising a native human serum albumin that is not regarded as exogenous by the subject, and they do not teach or suggest a conjugate comprising a linker that can be cleaved intracellularly. The mere fact that the single components of the claimed conjugate, *i.e.*, a human serum albumin, an azo-bond containing linker, and various active substances, may be known in the art does not render the conjugate as a whole obvious.

Srinivasan relates to conjugates comprising a targeting substance and a diagnostic/therapeutic agent joined by a stabilized Schiff base or hydrazone linkage. Applicants respectfully submit that the conjugates taught by Srinivasan are completely unrelated to the conjugates of the present invention. As correctly observed by the Examiner, the conjugates disclosed in Srinivasan comprise a Schiff base linkage, rather than a azo group linkage. The Examiner asserts that it would be obvious to simply substitute the Schiff base linkage by an azo bond. Applicants respectfully disagree.

First, it is noted that a Schiff base linkage is chemically totally different from an azo group, *i.e.*, a Schiff base entails an "-N=C<" bond, whereas an azo group is a "-N=N-" bond. Thus, a Schiff base linkage allows for three substituents, one at the N and one at the C, while the azo group allows only for two substituents. Accordingly, a Schiff base cannot be simply substituted by an azo group. Second, the physical and chemical characteristics of a stabilized Schiff base and an azo bond are entirely different due to their different chemical make-up. The Schiff base is composed of a nitrogen and a carbon, while the azo bond is a linkage of two nitrogen atoms. While a Schiff base would be expected to be stable in an intracellular environment, the azo linkage of the presently claimed conjugates is cleaved within a cell.

Neither of the cited secondary references cure the shortcoming of Srinivasan. ***Spector*** has been cited as allegedly disclosing the use of azo linkers to link active substances to albumin and suggesting the use of human serum albumin as the albumin. *See*, Office Action, at page 4. However, while Spector discloses the use of a diazophenylcarbonyl linking group, it does not teach using an azo linkage to link a chemotherapeutic agent or a photoactive substance to a human serum albumin. As pointed out, *supra*, given the differences in the chemical nature of a Schiff base, as employed by Srinivasan, and an azo group, the Schiff base of the Srinivasan conjugates could not simply be substituted by the diazophenylcarbonyl linking group disclosed in Spector. Therefore, a combination of Srinivasan and Spector does not teach or suggest the claimed conjugates.

Wong has been cited as showing a typical structure of an azo compound, which allegedly "reads on the structure of claim 18" and for teaching that a variety of different linkers are available to one of ordinary skill in the art. *See*, Office Action, at page 4. However, Applicants respectfully submit that the teaching of Wong does not cure the deficiencies of Srinivasan and Spector. While Wong may show the "-N=N-" structure of an azo bond, it does not teach the use of an azo linkage to link a chemotherapeutic agent or a photoactive substance to a human serum albumin. Again, given the differences between the chemical nature of a Schiff base and an azo group, the Schiff base of the Srinivasan conjugates could not simply be substituted by the azo bond shown in Wong. Therefore, a combination of Srinivasan, Spector and Wong does not teach or suggest the claimed conjugates.

There Is No Suggestion Or Motivation To Combine The References. Even assuming that the cited references in combination would suggest the claimed

invention, Applicants submit that the references have not been properly combined. In order to render the claimed invention obvious, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or ***motivation*** for the skilled artisan to modify or combine the references. *In re Fine*, 837 F.2d 1071, 1074 (1988). The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 733 F.2d 900, 902.

Nothing in either of the cited references contains anything that suggests the existence of, much the use in combination with, the other reference. The cited references are not obviously related to each other, and nothing contained in any of them suggests combining the references to produce the claimed result. Absent the teaching of the Applicants' Specification, one of ordinary skill in the art would not contemplate to combine the cited references. In fact, the only way to come up with the Examiner's proposed combination of references is to work backward from the Applicants' disclosure, using it as a template for hindsight reconstruction to discover a potentially useful combination of references. Combining references in order to achieve the claimed invention, when the references fail to suggest or imply the combination, amounts to the impermissible use of hindsight reasoning (*see* M.P.E.P. § 2145(X)(A)).

Srinivasan relates to conjugates comprising a targeting substance and a diagnostic/therapeutic agent joined by a Schiff base. Spector relates to a sensitive radioimmunoassay for chlorpromazine. Wong is a text book entitled "Chemistry of Protein Conjugation and Cross Linking." There is nothing in the cited references suggesting to combine the cited references to replace the Schiff base of the conjugates

disclosed in Srinivasan by an azo bond disclosed in Wong or Spector. Thus, neither reference provides the motivation or suggestion to combine them that is required by the law. For this additional reason, the presently claimed invention cannot be obvious over Srinivasan, Spector and Wong.

In view of the above, the Examiner has not met her burden of establishing a *prima facie* case of obviousness. First, the combination of Srinivasan, Spector and Wong does not teach or suggest the claimed invention. Furthermore, the cited references have not been properly combined. The proposed combination of references can only be achieved using hindsight reconstruction, starting from the disclosure of the Applicants and working backward. Therefore, Applicants respectfully request that the rejection of Claims 4, 5, 15, 17, 18, 23, 26, 27, 32, 38, 42, and 43 under 35 U.S.C. § 103(a) as being obvious over Srinivasan, Spector and Wong be withdrawn.

CONCLUSION

In view of the above amendments and remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 493-4935. The commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-1150 (order no.

8484-084-999) for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

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Enclosures